



**University of  
Zurich**<sup>UZH</sup>

**Zurich Open Repository and  
Archive**

University of Zurich  
Main Library  
Strickhofstrasse 39  
CH-8057 Zurich  
[www.zora.uzh.ch](http://www.zora.uzh.ch)

---

Year: 2012

---

## **Reconsidering GHB: orphan drug or new model antidepressant?**

Bosch, O G ; Quednow, Boris B ; Seifritz, E ; Wetter, T C

**Abstract:** For six decades, the principal mode of action of antidepressant drugs is the inhibition of monoamine re-uptake from the synaptic cleft. Tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs) and the new generation of dual antidepressants all exert their antidepressant effects by this mechanism. In the early days of the monoaminergic era, other efforts have been made to ameliorate the symptoms of depression by pharmacological means. The gamma-aminobutyric acid (GABA) system was and possibly still is one of the main alternative drug targets. Gammahydroxybutyrate (GHB) was developed as an orally active GABA analogue. It was tested in animal models of depression and human studies. The effects on sleep, agitation, anhedonia and depression were promising. However, the rise of benzodiazepines and tricyclic antidepressants brought GHB out of the scope of possible treatment alternatives. GHB is a GABA(B) and GHB receptor agonist with a unique spectrum of behavioural, neuroendocrine and sleep effects, and improves daytime sleepiness in various disorders such as narcolepsy, Parkinson's disease and fibromyalgia. Although it was banned from the US market at the end of the 1990s because of its abuse and overdose potential, it later was approved for the treatment of narcolepsy. New research methods and an extended view on other neurotransmitter systems as possible treatment targets of antidepressant treatment brought GHB back to the scene. This article discusses the unique neurobiological effects of GHB, its misuse potential and possible role as a model substance for the development of novel pharmacological treatment strategies in depressive disorders.

DOI: <https://doi.org/10.1177/0269881111421975>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-52636>

Journal Article

Accepted Version

Originally published at:

Bosch, O G ; Quednow, Boris B ; Seifritz, E ; Wetter, T C (2012). Reconsidering GHB: orphan drug or new model antidepressant? *Journal of Psychopharmacology*, 26(5):618-628.

DOI: <https://doi.org/10.1177/0269881111421975>

# **Reconsidering GHB: orphan drug or new model antidepressant?**

Oliver G. Bosch, Boris B. Quednow, Erich Seifritz, Thomas C. Wetter

*Clinic of Affective Disorders and General Psychiatry,  
University Hospital of Psychiatry, University of Zurich, Switzerland*

Review article to be submitted to

***Journal of Psychopharmacology***

Revised Version: June, 28<sup>th</sup>, 2011

Word count main text: 5300

Word count abstract: 242

Number of references: 162

Number of tables: 0

Number of figures: 1

## **Corresponding author:**

Oliver G. Bosch, MD

Clinic of Affective Disorders and General Psychiatry

Psychiatric University Hospital Zurich

Lenggstrasse 31, PO Box 1931, Zurich, Switzerland

Phone: +41 (0) 44 384 23 15

Fax: +41 (0) 44 383 44 56

Mail: [oliver.bosch@puk.zh.ch](mailto:oliver.bosch@puk.zh.ch)

## Abstract

For six decades, the principal mode of action of antidepressant drugs is the inhibition of monoamine re-uptake from the synaptic cleft. Tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs) and the new generation of dual antidepressants all exert their antidepressant effects by this mechanism. In the early days of the monoaminergic era, other attempts have been made to ameliorate symptoms of depression by pharmacological means. The gamma-aminobutyric acid (GABA) system was and possibly still is one of the main alternative drug targets. Gammahydroxybutyrate (GHB) was developed as an orally active GABA analogue. It was tested in animal models of depression and human studies. The effects on sleep, agitation, anhedonia and depression were promising. But the rise of benzodiazepines and tricyclic antidepressants brought GHB out of scope of possible treatment alternatives. GHB is a GABA<sub>B</sub> and GHB receptor agonist with a unique spectrum of behavioral, neuroendocrine and sleep effects, and improves daytime sleepiness in various disorders such as narcolepsy, Parkinson's disease and fibromyalgia. Although it was banned from the US-market end of the 1990-ies because of its abuse and overdose potential, it later was approved for the treatment of narcolepsy. New research methods and an extended view on other neurotransmitter systems as possible treatment targets of antidepressant treatment brought GHB back to the scene. This article discusses the unique neurobiological effects of GHB, its misuse potential and possible role as a model substance for the development of novel pharmacological treatment strategies in depressive disorders.

## Introduction

Gammahydroxybutyrate (GHB) was first synthesized by Henri Laborit in 1960, who aimed to create an orally active GABA analogue (Laborit et al., 1960). The sedating and narcotic effects of the compound led to its first use in anaesthesia and later in psychiatry (Langlois et al., 1960). Early studies reported anxiolytic and antidepressant effects of GHB in psychiatric patients. GHB was well tolerated in these patients, dizziness and nausea being the most limiting adverse effects (Danon-Boileau et al., 1962; Rinaldi et al., 1967). Its unique effects on sleep parameters were recognized early on. GHB seemed to induce a close-to-physiological sleep pattern with an increase in slow wave sleep (SWS) in humans (Mamelak et al., 1973). As benzodiazepines and tricyclic antidepressants were increasingly being prescribed, GHB was mainly used and studied in basic research. In the 1980ies GHB was available on the US market as a food supplement. It was abused by bodybuilders because of its stimulating effects on growth hormone release and thus its suspected anabolic potency. The US Food and Drug Administration (FDA) banned the drug in 1990 after cases of intoxication had occurred. As the abuse of the drug went on, the US government put it under narcotics law (Schedule I). However, GHB was approved for the treatment of narcolepsy with cataplexy in the US in 2002 and in Europe in 2005 (Carter et al., 2009). Furthermore, in Italy GHB is used and extensively studied in the treatment of alcohol addiction and craving (for review see Addolorato et al., 2009; and Leone et al., 2010).

*- Figure 1 about here -*

The contemporary focus on biological markers of depression as indicators of the treatment response and as targets of antidepressant therapy, has led to new interest in GABAergic substances and, thus, GHB (Mamelak, 2009).

## Neuropharmacology of GHB

GHB is an endogenous short fatty acid and a GABA metabolite that is present mainly in the hypothalamus and the basal ganglia in the mammal brain (Bessman and Fishbein, 1963; Snead and Morley, 1981). However, the highest concentrations can be found in peripheral body tissues such as the kidneys and brown fat (Nelson et al., 1981). The cerebral concentrations of GHB are approximately 0.1% of the concentrations of GABA (Maitre, 1997).

GHB has been described as an endogenous neurotransmitter due to the presence of specific G-protein coupled high and low affinity receptors ( $Kd1 = 30\text{-}580\text{ nmol/l}$  and  $Kd2 = 2.3\text{-}16\text{ }\mu\text{mol/l}$ ) and the specificity of the GHB antagonist NCS-382 (Benavides et al., 1982; Schmidt et al., 1991; Snead, 2000). Although various effects on several neurotransmitter systems have been reported, the precise physiological function of GHB remains a matter of debate (Wong et al., 2004; Crunelli et al., 2006; Andresen et al., 2011). Protective functions have been postulated, as GHB was shown to reduce the harmful effects of hypoxia and oxidative stress on various tissues in vitro and in vivo (e.g. heart, skeletal muscle, pancreatic  $\beta$  cells, lung, liver, gut, kidney and brain) (for review see Mamelak, 2007). However, later studies also showed induction of oxidative stress by GHB and its precursors in cerebral cortex of rats (Sgaravatti et al., 2007; 2009).

GHB is orally active and rapidly absorbed, while bioavailability is only about 25% (Palatini et al., 1993). Dose administration after high-fat meals significantly reduces bioavailability of the drug (Borgen et al., 2003). GHB shows nonlinear pharmacokinetics. Peak plasma concentrations are reached within 20 to 50 minutes, correlating with subjective effects, while plasma half-life is about 30 to 40 minutes (Ferrara et al., 1992; Scharf et al., 1998; Borgen et al., 2004; Brenneisen et al., 2004; Abanades et al., 2006). Endogenous and exogenous GHB is rapidly and completely converted into  $\text{CO}_2$  and  $\text{H}_2\text{O}$  through the tricarboxylic acid cycle

(Krebs cycle) (Maitre, 1997). Excretion happens through urine, breath and oral fluids (Brenneisen et al., 2004).

Presumably, exogenous supraphysiological concentrations of GHB produce qualitatively different neuronal actions than those produced by endogenous GHB concentrations. Despite its high affinity to GHB receptors, most of its effects are mediated by an agonist action at GABA<sub>B</sub> receptors after exogenous application (Engberg and Nissbrandt, 1993). GABA<sub>B</sub> antagonists reverse and GABA<sub>B</sub> agonists mimic core effects of GHB on both the neuronal and behavioral level (Engberg and Nissbrandt, 1993; Kaupmann et al., 2003). However, the effects of GHB and the specific GABA<sub>B</sub> agonist baclofen can be differentiated experimentally (Mathivet et al., 1997; Wong et al., 2004). Thus, high concentrations of GHB might act on the high affinity GHB receptor and on the GABA<sub>B</sub> receptor, respectively.

GHB was reported to increase dopamine and norepinephrine levels in a biphasic mode. First, the release of both neurotransmitters is inhibited, which leads to a neuronal accumulation. Then, the release of the accumulated dopamine and norepinephrine is stimulated, resulting in an increased temporary output of these neurotransmitters (Hechler et al., 1991; Maitre, 1997; Pardi and Black, 2006). Moreover, an increase in serotonin synthesis and metabolism has been shown (Gobaille et al., 2002; Szabo et al., 2004). Although some effects of GHB can be antagonized by naloxone, thus indicating a certain opioidergic effect of the drug, no direct stimulation of mu, delta and kappa receptors could be shown (Hechler et al., 1991; Feigenbaum and Howard, 1996; Feigenbaum and Simantov, 1996). Furthermore, the cholinergic system is affected by GHB (Volpi et al., 2000), as well as the synthesis and release of hormones such as neurosteroids, growth hormone and cortisol, as described in detail below.

## **Subjective effects, medical use and abuse**

In the literature there is a relatively small but growing body of work investigating the subjective effects of GHB intoxication and the reasons underlying its illicit use. The subjective effects of GHB constitute a continuum between relaxation, increased social interaction, euphoria and increased well-being in lower doses (10 mg/kg) up to profound sedation and deep sleep in higher doses (30-50 mg/kg) (Delay et al., 1965; Rosen et al., 1997; Iten et al., 2000; Barker et al., 2007). Doses over 50 mg/kg may cause coma and respiratory depression (Metcalf et al., 1966). Emergency ward patients with severe coma (Glasgow Coma Scale [GCS] 3-8) showed GHB serum levels that ranged from 72 to 430 mg/l. They abruptly regained consciousness after levels fell under 75 to 150 mg/l (Sporer et al., 2003; Van Sassenbroeck et al., 2007). Illicit GHB users describe its subjective effects as comparable to both alcohol and methylenedioxymethamphetamine (MDMA, “ecstasy”), with disinhibition, drowsiness, euphoria, and enhancing sensuality and empathogenesis. This is the reason why it was called “liquid ecstasy” in the club scene (Galloway et al., 2000). In an online survey (n = 189) the most frequently reported reasons for GHB use were for recreation purposes (18.3%), to enhance sex (18.3%), to be sociable (13.1%), and to explore altered states of consciousness (13.1%) (Sumnall et al., 2008). These data confirm previous studies concerning the motivations of illicit GHB use (Miotto et al., 2001; Degenhardt et al., 2002; Barker et al., 2007). The influence of GHB on sex is a popular theme throughout consumers of the drug. Many aspects of sexuality are said to be enhanced, such as sexual desire, arousal, and activity. A qualitative focus group study using structured interviews and questionnaires including 51 GHB users could confirm these anecdotal reports (Barker et al., 2007).

Sodium oxybate is the international drug name for the sodium salt of GHB. In research the terms are used synonymously. In numerous international multicenter trials, GHB has been shown to be an unparalleled treatment for the complex of narcolepsy symptoms: sleepiness,

sleep fragmentation and cataplexy (Xyrem-US, 2002; Xyrem-International, 2005). GHB oral solution (no tablet form available) is merchandized as Xyrem® in the U.S., Canada and Europe (incl. Switzerland). In these countries it is the first line treatment for excessive daytime sleepiness and cataplexy in patients with narcolepsy. GHB is approved in Germany as an anaesthetic, Somsanit® and is approved in Austria and Italy for the treatment of alcohol withdrawal as Alcover®, while it is also used off-label for opiate withdrawal (Gallimberti et al., 1994).

Beneficial therapeutic effects in schizophrenia (Kantrowitz et al., 2009), posttraumatic stress disorder (Schwartz, 2007), affective disorders (Berner, 2008; Mamelak, 2009), excessive daytime sleepiness in fibromyalgia (Scharf et al., 2003) as well as in Parkinson's disease (Ondo et al., 2008) have also repeatedly been reported. GHB is a robust enhancer of slow wave sleep in patients with sleep disorders with excessive daytime sleepiness and in healthy subjects (Van Cauter et al., 1997). Finally, GHB was shown to have a favourable safety profile both in therapeutic and experimental settings (Kantrowitz et al., 2009; Leone et al., 2010).

In a medical or scientific context, the risk of acute toxicity is low. Multicenter studies and post marketing surveillance for GHB (Xyrem) suggested a very low incidence of unexpected side effects even in long term use (Xyrem-US, 2002; Xyrem-International, 2005; Wang et al., 2009). In addition to the regular spontaneous adverse event reporting system, a distribution and post-marketing surveillance system called Xyrem Success Program was created and a Post-Marketing Evaluation Program (PMEP) was implemented to guarantee the safe use of the drug (Fuller et al., 2004). Between 2002 and 2008 approximately 26.000 patients worldwide were treated with Xyrem, and approximately 600.000 bottles of the drug were distributed. The most frequently reported adverse events were nausea (2.2%), insomnia (1.4%), headache (1.4%), dizziness (1.3%) and vomiting (1.0%). Five incidents (0.0009%) of diversion of Xyrem bottles were reported (Wang et al., 2009). Cases of development of addiction and deaths related to Xyrem treatment are discussed below. Residual toxicity of



GHB is very small as it is rapidly metabolized to CO<sub>2</sub> and H<sub>2</sub>O as described above.

Regarding the often supposed concern about the potential addictive effect of GHB (Galloway et al., 1997; Nicholson and Balster, 2001), animal studies showed a relatively low reinforcing effect compared to barbiturates and benzodiazepines. GHB and its precursors 1,4-butanediol (BDL) and gamma-butyrolactone (GBL) were not able to substitute for pentobarbital, methohexital, midazolam, diazepam or flumazenil in rhesus monkeys. Self-administration was lower than with these substances and the total maintained self-administration was marginally above saline levels (Woolverton et al., 1999; McMahon et al., 2003). In humans, a clear differentiation has to be made between illicit uncontrolled and medically supervised use of the substance. GHB is abused by a small percentage of the population (< 1%) as a recreational drug in a home setting or as a "club drug" (Sumnall et al., 2008). Unlike certain media reports suggested, the major type of GHB consumer was shown to be well-educated, financially secure and fully employed, living a stable, middle-class urban life (Degenhardt et al., 2002; Barker et al., 2007). In humans, the abuse liability was shown to be comparable to the benzodiazepine flunitrazepam (Abanades et al., 2007) and intermediate between triazolam and pentobarbital (Carter et al., 2006). GHB withdrawal after chronic and heavy use often may be accompanied by severe complications such as hypertonia and delirium and requires high doses of medication such benzodiazepines, antihypertensives and antipsychotics. Intensive care treatment comparable to alcohol or benzodiazepine withdrawal may be necessary (van Noorden et al., 2009). After abrupt discontinuation of GHB in patients with narcolepsy, 17% developed symptoms such as anxiety, dizziness, insomnia, and somnolence. Most of the symptoms were interpreted as recurring narcoleptic symptoms or mild withdrawal symptoms. Therefore, it is suggested to slowly taper off the drug if it is intended to be stopped (Xyrem-US, 2003).

Cases of physical dependence have been reported in recreational illicit GHB users, but exact statistical analysis remains difficult as the estimated number of unreported non-dependent users is not known. Consequently, the risk for developing an addiction after regular illicit

GHB use shows high variations in the according studies. While 4% of GHB users presented addiction to GHB in an Australian sample with 76 subjects, in another study with a small sample size of 41 subjects, 9 of them (21%) reported to be physically dependent on the drug. In both studies, most GHB dependent subjects had histories of polydrug abuse including MDMA, cannabis, cocaine, and methamphetamine (Miotto et al., 2001; Degenhardt et al., 2002; Carter et al., 2009). Compared to this, risk of substance dependency or withdrawal syndrome after the use of therapeutically applied GHB is low. In a post-marketing surveillance study, one case for every 3300 to 6500 patients treated, or approximately 0.031 to 0.015 %, developed an addiction that fulfilled the DSM-IV criteria (Wang et al., 2009). Moreover, marked differences in patterns of use and dosing of GHB may be found in medical and illicit use. While GHB is given in doses of 4.5 to 9 g in two doses at night in a medical context, illicit use occurs with frequent dosing of 5 to 30 g GHB throughout day and night (Barker et al., 2007; Craig et al., 2000; Degenhardt et al., 2003; Miotto et al., 2001; Sumnall et al., 2008; Wojtowicz et al., 2008).

As the therapeutic dose range of GHB is quite narrow, overdoses and the combination with central nervous system (CNS) depressants such as alcohol produce serious risks. Rapid loss of consciousness with coma necessitating intubation and intensive care is the most dreaded adverse effect of an acute GHB intoxication. Although cases of GHB-related death were reported from most of the countries where the drug is used illicitly, the relative and total numbers of fatal cases appear small (Andresen et al., 2008; Munir et al., 2008). In a Swedish sample of 23 deaths after GHB overdose, which occurred between the years 2000 and 2007, a coingestion of other substances or alcohol was found in 91% (Knudsen et al., 2010). Another case series of 226 GHB associated deaths, which occurred between 1995 and 2005 in the USA, Canada and the UK, showed absence of co-intoxicants in only 35% of the subjects (Zvosec et al., 2010). Of 1.419 drug related deaths in the UK in 2009, 6 (0.4%) were due to GHB alone and 15 (1%) due to GHB in combination with other drugs. In comparison, Alcohol was implicated in 447 (31.5%) and Heroin in 689 (49.2%) cases of drug related

death (Ghodse et al., 2010). One problem of interpreting post mortem GHB concentrations in blood and urine is the endogenous production of GHB, which can lead to false positive effects. Blood concentrations less than 30 mg/l and urine concentrations of less than 20 mg/l are suspected to be due to endogenous release of GHB. Anyway, post-mortem GHB concentrations up to 197 mg/l could be detected in cases without previous ingestions of the drug (Elliot, 2001; Elliott, 2004). These concentrations overlap with the post mortem serum levels of GHB-related deaths, which showed a range between 18 to 4400 mg/l (Knudsen et al., 2010; Zvosec et al., 2010). Although most GHB fatalities happened in cases of illicit use, four deaths after medical use were also reported (Akins et al., 2009; Zvosec et al., 2009).

Taken animal and human data together, the addictive potential of illicitly used GHB is comparable to alcohol and benzodiazepines and needs to be taken seriously (Gonzalez and Nutt, 2005). In contrast, the cumulative post marketing and clinical experience indicates a very low risk of abuse of therapeutically applied GHB (Wedin et al., 2006; Kantrowitz et al., 2009).

## **GABA<sub>B</sub> receptors and GHB in depression: animal and human studies**

The GABAergic system is the principal mediator of neuronal inhibition in the brain.

Dysfunction of GABA neurotransmission has been proposed to play an important role in psychiatric disorders, including anxiety and depression (Kalueff and Nutt, 2007). While the link between GABA and anxiety is clearly established, the importance of GABAergic dysfunction in the aetiology and course of depression remains unclear. Animal studies showed that alterations of GABA<sub>B</sub> receptor function cause antidepressant-like behaviour (Cryan and Slattery, 2010). Some human studies indicate a beneficial effect of the GABA<sub>B</sub> agonist baclofen on depression symptoms (Krupitsky et al., 1993; Drake et al., 2003).

Baclofen is further known to impair cognition by its sedative effect and to increase concentrations of both growth hormone (Cavagnini et al., 1977) and cortisol (Morosini et al., 1980).

Shortly after the discovery of GHB by Laborit in 1960, the drug was tested in clinical psychiatric populations. As GHB was meant to induce an almost physiological or natural sleep, it was applied to sedate patients with alcohol withdrawal syndrome and severe anxiety states. The favourite mode of application was i.v. or s.c., using doses between 2 to 5 g (Laborit et al., 1960; Langlois et al., 1960; Danon-Boileau et al., 1962). Also GBL, a precursor of GHB, was tested successfully in the treatment of alcohol withdrawal and psychotic states with agitation and anxiety (Benda et al., 1960). In a study with 15 psychiatric patients, mainly with depression and anxiety disorders, GHB application of 2 g i.v. three times daily lead to a good clinical improvement of most patients. The drug was given over a period of 4 to 15 days. Reported general effects were relaxation and euphoria instantly after administration and a normalization of affective symptoms in the course of the treatment. A marked improvement of interpersonal contact was the main behavioral change, resulting in an amelioration of the psychotherapeutic alliance. The limiting side effect was nausea with

vomiting, which led to discontinuation of the treatment in three cases (Danon-Boileau et al., 1962). In another study, GHB was used either to induce sleep therapy (n = 10) or as tranquilizing agent to facilitate psychotherapy (n = 20) in patients with various psychiatric disorders (schizophrenia, depression, anxiety) (Ducouedic et al., 1964). The drug showed a high efficacy for both treatments. Sleep induction was reliable and safe and patients woke up easily without being hung over. A robust reduction of anxiety could be achieved in wake patients with three injections of GHB daily. The authors underlined the prosocial and contact facilitating effects of the drug, as they enabled psychotherapeutic dialogs in patients previously inhibited by their severe psychopathology.

The first systematic though not placebo-controlled study with GHB in patients with depressive disorder was performed by Rinaldi and colleagues (1967). Single evening i.v. injections of 4 g GHB repeated for 3 to 12 days were used as tentative therapy in a group of 30 female depressed patients. Symptoms of depression were measured by the Wechsler Depression Rating Scale (W-DRS) and the Zung Self-rating Depression Scale (Z-SDS). The best response was seen in core depression symptoms such as depressed mood, insomnia, loss of appetite and fatigue. After a sudden partial improvement of symptoms during the first 24 h, complete remission was achieved at the end of treatment in 24 patients after only 12 days (Rinaldi et al., 1967).

In animal models of depression, which were sensitive to antidepressive effects of other pharmacological agents, GHB and its analogues produced antidepressant-like changes in behaviour and neurotransmitter release (Davies, 1978; Zerbib et al., 1992). GBL showed a biphasic behavioral effect in rats. Initially, locomotor activity of the animals was reduced after intraperitoneal injections of 100 and 200 mg/kg of the drug. This reduction was then followed by a period of hyperactivity. This increase of activity was probably due to a release of dopamine, as the indirect dopamine receptor agonist benztropine (25 mg/kg) potentiated, while the dopamine D2-receptor antagonist  $\alpha$ -flupenthixol (50  $\mu$ g/kg) blocked the effect (Davies, 1978). This biphasic effect on the neuronal dopaminergic system was hypothesized

to be a neurobiological correlate to the initially sedative and then euphoric/mood augmenting properties of GHB in depressed patients. These results were confirmed by Zerbib and colleagues (1992) in mice after acute and chronic application of 2 mmol/kg GHB i.p.. Additionally, striatal dopamine concentrations and immobility in the behavioral despair test (BDT) were assessed. A potential antidepressant effect could be shown, which was similar to the effect of imipramine but not to the effects of antipsychotics or anxiolytics (Zerbib et al., 1992).

Taken animal and limited human data together, GHB appears as a compound with unique pharmacological properties and potential antidepressant effects. In the first place, GHB acts as a tranquilizing agent, showing dose-dependent effects ranging from increase of sociability and anxiolysis to sleep induction. Apart of these, mainly GABAergic mechanisms, secondary effects on the monoaminergic systems (serotonin, norepinephrine and dopamine) might play a role in the antidepressant potential, which was described in the early studies. Here, GHB showed effectiveness in core effects of depression, such as fatigue, anhedonia and depressed mood. To complete the spectrum of the pharmacological properties of GHB, its distinct neuroendocrine effects have to be considered.

## **Neuroendocrine effects of GHB**

During the past decades, strong efforts have been made to identify biological alterations in depression, which could serve either as diagnostic or prognostic markers or as therapeutical targets. Neuroendocrine, genetic and sleep parameters were investigated for their potential use as biomarkers of depression. In this regard, the most promising results were achieved for neuroendocrine and sleep measures (Kupfer, 1978; Holsboer and Ising, 2010; Steiger and Kimura, 2010).

Although not specific, neuroendocrine alterations might have a high sensitivity for depression (Heuser et al., 1994). A common finding during a depressive episode is a dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis (Ising et al., 2005; Ising et al., 2007). A chronic hyperactivity of the HPA axis results in increased plasma concentrations of the stress hormones corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), adrenocorticotrophic hormone (ACTH) and cortisol. These hormones induce psychopathological changes such as increased anxiety, fatigue, exhaustion and memory impairment (Holsboer and Ising, 2010). However, morphological alterations of brain structures can also be detected in patients with stress-related depression. Loss of hippocampus volume is a prominent finding, which is hypothesized to be due to chronic cortisol exposure in case of HPA hyperactivity (McEwen, 2001; Pruessner et al., 2010).

Antidepressants such as citalopram, venlafaxine, reboxetine and mirtazapine are known to exert a normalizing effect on a dysregulated HPA activity, which partially correlates with psychopathological improvement. It was posited, that this effect may be important for the antidepressant property of such agents (Schule, 2007). Moreover, neurosteroids and oxytocin are discussed to play a critical role in the regulation of social and sexual behaviour, as well as the neurobiology of depression (Scantamburlo et al., 2009; Reddy, 2010; Schule et al., 2010). GHB was found to interact with HPA axis activity and neurosteroidogenesis (Barbaccia, 2004; Nava et al., 2007) and was hypothesized to have an impact on oxytocinergic brain structures (McGregor et al., 2008). Considering an antidepressive potential of GHB, these interactions are of particular interest if one assumes GHB to be a model antidepressant compound with GABAergic, monoaminergic and neuroendocrine mechanisms of action.

### *Neurosteroids*

Neurosteroids such as the centrally synthesized progesterone analogues allopregnanolone ( $3\alpha,5\alpha$ -THP) and allotetrahydrodeoxy-corticosterone ( $3\alpha,5\alpha$ -THDOC), have prosexual,

anxiolytic and stress reducing effects. Comparable to benzodiazepines, these effects are mainly due to an agonist action at GABA<sub>A</sub> receptors (Rupprecht and Holsboer, 1999; Frye et al., 2009). In rats, allopregnanolone reduces the reactivity to stress by inhibiting central CRH release. At the same time, cerebral expression of mineralocorticoid (MR) and glucocorticoid receptors (GR) and of AVP is reduced (Patchev et al., 1994; Patchev et al., 1996). Moreover, allopregnanolone showed antidepressant-like effects in mice, which was potentiated by serotonergic agents such as fluoxetine and fenfluramine (Khisti and Chopde, 2000; Khisti et al., 2000). Patients suffering from major depression and co-morbid depressive symptoms in posttraumatic stress disorder, show decreased plasma and CSF concentrations of 3 $\alpha$ ,5 $\alpha$ -THP (Romeo et al., 1998; Uzunova et al., 1998; Rasmusson et al., 2006). Fluoxetine and mirtazapine treatment could normalize these neurosteroid imbalances (Uzunova et al., 1998; Schule et al., 2006). Deficits in neurosteroidogenesis were hypothesized to play a significant role in the pathophysiology of depression and posttraumatic stress disorder (Rupprecht and Holsboer, 1999; Pinna, 2010). Synthetic neurosteroids or pharmacological agents that modulate neurosteroidogenesis are discussed as novel therapeutic strategies in depression and anxiety disorders (Schule et al., 2011). Interestingly, 3 $\alpha$ ,5 $\alpha$ -THP and 3 $\alpha$ ,5 $\alpha$ -THDOC are dose-dependently released after GHB application in rats. The time course of the elevated neurosteroid brain concentrations correlates with the GHB-induced sedation (Barbaccia, 2004). Both, the sedation and the increased neurosteroidogenesis are inhibited by GABA<sub>B</sub> receptor antagonists (Carai et al., 2001; Barbaccia et al., 2002). It could be shown, that the sedative effect of GHB in rats is due to a rise of brain concentration of the neurosteroids 3 $\alpha$ ,5 $\alpha$ -THP and 3 $\alpha$ ,5 $\alpha$ -THDOC (Barbaccia et al., 2005).

### *Oxytocin*

Another hormone of primary interest for the explanation of emotional and behavioral effects of GHB is the “binding-hormone” oxytocin (OT), which is a peptide hormone and a functional antagonist of the stress hormone AVP. OT regulates social affiliation and social recognition in many species and modulates anxiety, mood and aggression. OT inhibits the HPA axis



under stress, reduces amygdala hyperactivity in depressed patients and enhances social behaviour (Heinrichs et al., 2003; Zak et al., 2007; Meyer-Lindenberg, 2008). However, a direct antidepressant effect of OT was not studied to date (Stein, 2009). It is hypothesized that GHB may induce its characteristic prosocial and prosexual effects due to an activation of brain OT systems. Social and sexual behaviour is facilitated by interactions of OT with the mesolimbic dopamine system (McGregor et al., 2008). GHB has a strong impact on dopamine release. Stimulation of OT neurons might be one of the mechanisms by which the drug modulates the dopaminergic tone. It could be shown that OT release is a core neuroendocrine feature of MDMA effects, which is correlated with the feeling of closeness, euphoria and loss of boundaries (Dumont et al., 2009). If this may also be the case for GHB, has not been studied in humans, yet. The prosocial properties of GHB are comparable to the ones of MDMA - without showing MDMA-related acute negative secondary effects such as hyperthermia, acute psychosis, panic attacks and insomnia (Karlsen et al., 2008). Moreover, GHB has anti-aggressive (Navarro et al., 2007; Pedraza et al., 2007) and anxiolytic properties (Schmidt-Mutter et al., 1998; Frawly and McMillan, 2008) and seems to be clearly prosexual (Degenhardt et al., 2002; Sumnall et al., 2008). An indicative for its OT-stimulating effects could be the former use of GHB to induce uterine contractions in childbirth (Geldenhuys et al., 1968). Regarding the putative role of GHB in the hormonal regulation of stress and depression, it is of particular interest that OT has an inhibitory effect on HPA activity (Uvnas-Moberg, 1998; Legros, 2001; Windle et al., 2004). Further studies are needed to understand the complex interactions of hormones in the regulation of affectivity and affective deficits and the various effects of GHB in this context.

### *Growth hormone and the HPA axis*

In the 1980ies GHB became popular among bodybuilders because of its capacity of stimulating growth hormone (GH) secretion. GH secretion after intake of GHB is due to stimulation of both specific pituitary GHB and cerebral GABA<sub>B</sub> receptors (Vescovi and Coiro, 2001). However, blocking of muscarinic cholinergic receptors with the anticholinergic agent

pirenzepine leads to a suppression of GHB-induced GH secretion in humans (Volpi et al., 2000). This indicates an important downstream effect of GHB on the cholinergic system. The GH stimulating effect of GHB seems to correlate with its capacity to induce slow wave sleep (Van Cauter et al., 1997).

The effects of GHB on the HPA axis were examined in several trials, but the results were controversial. Slow wave sleep is accompanied by a reduced HPA activity and an increase of GH secretion. Paradoxically, GHB induces deep sleep and seems to stimulate both cortisol and GH release. Under resting conditions GHB induces a stimulation of cortisol secretion in animals and humans (Oyama et al., 1969; Van Cauter et al., 1997; Meerlo et al., 2004). One case of hypercortisolism was reported following chronic illicit use of GHB (Razenberg et al., 2007). In contrast, GHB showed a lasting suppression of withdrawal associated hypercortisolism in alcoholic patients (Nava et al., 2007). Moreover, previous studies showed a smaller activation of the HPA axis under stress after GHB application (Korolev et al., 1979; Malyshev et al., 1981). These data suggest that GHB might normalize a dysregulated HPA axis (possibly by neurosteroidogenesis), while normal HPA activity might be altered by the drug.

## **GHB, sleep and residual symptoms of depression**

Major depression is associated with pronounced alterations in sleep architecture, such as SWS reduction, sleep fragmentation, and rapid-eye-movement (REM) sleep disinhibition (Kupfer, 1978; Borbely et al., 1984; Germain et al., 2004; Steiger and Kimura, 2010).

Interestingly and as mentioned before, GHB induces slow wave sleep (SWS) in healthy subjects and increases both SWS and sleep efficacy with concomitant reduction of daytime sleepiness in patients with narcolepsy, fibromyalgia and Parkinson's disease. This effect leads to a marked increase in social functioning and quality of life in these patients (Pardi and Black, 2006; Mamelak, 2009). However, the physiological nature of GHB-induced sleep

is still under debate (Meerlo et al., 2004; Vienne et al., 2010). In populations, which are specifically sensitive to REM-sleep induction such as older healthy subjects or patients with affective disorders or narcolepsy, GHB acutely exerts a facilitative effect on REM sleep (Mamelak et al., 1977; Broughton and Mamelak, 1980; Lapierre et al., 1990). A case report of a markedly reduced REM latency after GHB application in a patient in remission of major depressive disorder, led to the idea of using GHB REM-latency induction as a biological marker for depression (Lapierre et al., 1989). Monoaminergic insufficiency and cholinergic supersensitivity was accounted for reduced REM-latency in both, depression (Belmaker and Agam, 2008; Dilsaver, 1986; Janowsky et al., 1972) and narcolepsy (Nishino, 2007; Shiromani et al., 1987). Four to six weeks of treatment with GHB normalized the altered REM-latency in patients with narcolepsy (Mamelak et al., 2004). Mamelak (2009) stated that this improvement might be explained by the capacity of GHB to recover monoaminergic and cholinergic dysbalance, and that this mechanism might be also effective in mood disorders.

Despite scientific advances in the treatment of major depressive disorder, antidepressant first line agents yield only modest remission rates (Trivedi et al., 2006). One major problem is the presence of residual symptoms such as sleep disturbances, fatigue/daytime sleepiness and cognitive impairment (Kurian et al., 2009). These symptoms often precede depressive mood symptoms and persist after remission, exposing the patient to a higher risk for a new depressive episode (Judd et al., 2000). The pharmacological treatment of depression related sleep disorders can be especially challenging. Potent hypnotic agents such as benzodiazepines are limited by the risk of inducing tolerance or even addiction and sedating tricyclic antidepressants show an unfavourable side-effect profile (Becker, 2006; Becker and Sattar, 2009). Lastly, more recent and well-tolerated sedating antidepressants such as mirtazapine often generate hangovers and exacerbate daytime sleepiness, which is a disrupting symptom of depression itself (Baldwin and Papakostas, 2006). Treatment strategies that target fatigue and cognitive dysfunction often include psychostimulants such as methylphenidate, modafinil or atomoxetine. However, the tolerability of these agents

makes them undesirable treatment choices (Kurian et al., 2009). The almost typical patterns of sleep disturbances in depression, with concomitant daytime sleepiness make this syndrome a potential target for treatment with GHB. However, such a study has not been performed to date.

## Conclusions

Depression is still conceptualized as a state of monoaminergic insufficiency and cholinergic supersensitivity. Neuroendocrine dysbalances, such as HPA axis hyperactivity, neurosteroid and growth hormone deficiency, and sleep alterations including reduced slow wave sleep and REM-latency are discussed as biological markers of affective disorders. Most antidepressant drugs exert their effects via increasing the concentration of monoamines in the synaptic cleft. Recent research focussed on new targets for the pharmacological treatment of depression, such as the GABAergic system. GHB is a GABA<sub>B</sub> and GHB receptor agonist with specific effects on neuroendocrine and sleep parameters. It stimulates neurosteroidogenesis in animals and was shown to reduce HPA hyperactivity in humans. Given at night, slow wave sleep and growth hormone secretion are increased. In patients with narcolepsy, GHB normalizes sleep disturbances and reduces daytime sleepiness and cataplexy. This was attributed to the capacity of the drug to normalize monoaminergic and cholinergic tone. Although a certain potential for the treatment of depression was already suspected in early studies, an explicit impetus to examine the effects of GHB in affective disorders was given only recently. New GABA<sub>B</sub>/GHB receptor activating compounds might be developed, which share GHBs beneficial effects without having the same addictive and properties and with a broader therapeutic dose range. Given that GHB exerts its effects on several strongly linked neurobiological core clinical symptoms of depression such as anhedonia, social withdrawal and sleep disturbances, it might also serve as a model compound possibly leading to novel strategies in the treatment of affective disorders.

## Acknowledgements

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. All authors declared no biomedical conflict of interest.

## References

- Abanades S, Farre M, Barral D, et al. (2007) Relative abuse liability of gamma-hydroxybutyric acid, flunitrazepam, and ethanol in club drug users. *J Clin Psychopharmacol* 27: 625-638
- Abanades S, Farre M, Segura M, et al. (2006) Gamma-hydroxybutyrate (GHB) in humans: pharmacodynamics and pharmacokinetics. *Ann N Y Acad Sci* 1074: 559-576
- Addolorato G, Leggio L, Ferrulli A, et al. (2009) The therapeutic potential of gamma-hydroxybutyric acid for alcohol dependence: balancing the risks and benefits. A focus on clinical data. *Expert Opin Investig Drugs* 18: 675-686
- Akins BE, Miranda E, Lacy JM, et al. (2009) A multi-drug intoxication fatality involving Xyrem (GHB). *J Forensic Sci* 54: 495-496
- Andresen H, Aydin BE, Mueller A, et al. (2011) An overview of gamma-hydroxybutyric acid: pharmacodynamics, pharmacokinetics, toxic effects, addiction, analytical methods, and interpretation of results. *Drug Test Anal*
- Andresen H, Stimpfl T, Sprys N, et al. (2008) Liquid ecstasy - a significant drug problem. *Dtsch Arztebl Int* 105: 599-603
- Baldwin DS and Papakostas GI (2006) Symptoms of fatigue and sleepiness in major depressive disorder. *J Clin Psychiatry* 67 Suppl 6: 9-15
- Barbaccia ML (2004) Neurosteroidogenesis: relevance to neurosteroid actions in brain and modulation by psychotropic drugs. *Crit Rev Neurobiol* 16: 67-74
- Barbaccia ML, Carai MA, Colombo G, et al. (2005) Endogenous gamma-aminobutyric acid (GABA)(A) receptor active neurosteroids and the sedative/hypnotic action of gamma-hydroxybutyric acid (GHB): a study in GHB-S (sensitive) and GHB-R (resistant) rat lines. *Neuropharmacology* 49: 48-58
- Barbaccia ML, Colombo G, Affricano D, et al. (2002) GABA(B) receptor-mediated increase of neurosteroids by gamma-hydroxybutyric acid. *Neuropharmacology* 42: 782-791
- Barker JC, Harris SL and Dyer JE (2007) Experiences of gamma hydroxybutyrate (GHB) ingestion: a focus group study. *J Psychoactive Drugs* 39: 115-129
- Becker PM (2006) Treatment of sleep dysfunction and psychiatric disorders. *Curr Treat Options Neurol* 8: 367-375
- Becker PM and Sattar M (2009) Treatment of sleep dysfunction and psychiatric disorders. *Curr Treat Options Neurol* 11: 349-357
- Belmaker RH and Agam G (2008) Major depressive disorder. *N Engl J Med* 358: 55-68
- Benavides J, Rumigny JF, Bourguignon JJ, et al. (1982) A high-affinity, Na<sup>+</sup>-dependent uptake system for gamma-hydroxybutyrate in membrane vesicles prepared from rat brain. *J Neurochem* 38: 1570-1575
- Benda P, Deshaies G, Perles R, et al. (1960) Premier essai de la butyrolactone en clinique. *Ann medico psychol* 2: 770-775
- Berner JE (2008) A case of sodium oxybate treatment of tardive dyskinesia and bipolar disorder. *J Clin Psychiatry* 69: 862
- Bessman SP and Fishbein WN (1963) Gamma-Hydroxybutyrate, a Normal Brain Metabolite. *Nature* 200: 1207-1208
- Borbely AA, Tobler I, Loepte M, et al. (1984) All-night spectral analysis of the sleep EEG in untreated depressives and normal controls. *Psychiatry Res* 12: 27-33
- Borgen LA, Okerholm R, Morrison D, et al. (2003) The influence of gender and food on the pharmacokinetics of sodium oxybate oral solution in healthy subjects. *J Clin Pharmacol* 43: 59-65
- Borgen LA, Okerholm RA, Lai A, et al. (2004) The pharmacokinetics of sodium oxybate oral solution following acute and chronic administration to narcoleptic patients. *J Clin Pharmacol* 44: 253-257
- Brenneisen R, Elsohly MA, Murphy TP, et al. (2004) Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. *J Anal Toxicol* 28: 625-630
- Broughton R and Mamelak M (1980) Effects of nocturnal gamma-hydroxybutyrate on sleep/waking patterns in narcolepsy-cataplexy. *Can J Neurol Sci* 7: 23-31
- Carai MA, Colombo G, Brunetti G, et al. (2001) Role of GABA(B) receptors in the sedative/hypnotic effect of gamma-hydroxybutyric acid. *Eur J Pharmacol* 428: 315-321
- Carter LP, Pardi D, Gorsline J, et al. (2009) Illicit gamma-hydroxybutyrate (GHB) and pharmaceutical sodium oxybate (Xyrem): differences in characteristics and misuse. *Drug Alcohol Depend* 104: 1-10

- Carter LP, Richards BD, Mintzer MZ, et al. (2006) Relative abuse liability of GHB in humans: A comparison of psychomotor, subjective, and cognitive effects of supratherapeutic doses of triazolam, pentobarbital, and GHB. *Neuropsychopharmacology* 31: 2537-2551
- Cavagnini F, Invitti C, Di Landro A, et al. (1977) Effects of a gamma aminobutyric acid (GABA) derivative, baclofen, on growth hormone and prolactin secretion in man. *J Clin Endocrinol Metab* 45: 579-584
- Craig K, Gomez HF, McManus JL, et al. (2000) Severe gamma-hydroxybutyrate withdrawal: a case report and literature review. *J Emerg Med* 18: 65-70
- Crunelli V, Emri Z and Leresche N (2006) Unravelling the brain targets of gamma-hydroxybutyric acid. *Curr Opin Pharmacol* 6: 44-52
- Cryan JF and Slattery DA (2010) GABAB receptors and depression. Current status. *Adv Pharmacol* 58: 427-451
- Danon-Boileau H, Lavitry S, Lab P, et al. (1962) [Utilization in psychiatry of gamma-OH]. *Presse Med* 70: 2205-2207
- Davies JA (1978) The effect of gamma-butyrolactone on locomotor activity in the rat. *Psychopharmacology (Berl)* 60: 67-72
- Degenhardt L, Darke S and Dillon P (2002) GHB use among Australians: characteristics, use patterns and associated harm. *Drug Alcohol Depend* 67: 89-94
- Degenhardt L, Darke S and Dillon P (2003) The prevalence and correlates of gamma-hydroxybutyrate (GHB) overdose among Australian users. *Addiction* 98: 199-204
- Delay J, Deniker P, Perier M, et al. (1965) [Neuro-psychic effects of gamma-hydroxybutyric acid by oral route and by venous route]. *Encephale* 54: 546-554
- Dilsaver SC (1986) Pathophysiology of "cholinoceptor supersensitivity" in affective disorders. *Biol Psychiatry* 21: 813-829
- Drake RG, Davis LL, Cates ME, et al. (2003) Baclofen treatment for chronic posttraumatic stress disorder. *Ann Pharmacother* 37: 1177-1181
- Ducouedic H, Ducouedic A and Voisse M (1964) [Contribution to the Study of Sodium 4-Hydroxybutyrate (4ho) in the Treatment of Acute Anxiety States]. *Agressologie* 5: 73-86
- Dumont GJ, Sweep FC, van der Steen R, et al. (2009) Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci* 4: 359-366
- Elliot S (2001) The presence of gamma-hydroxybutyric acid (GHB) in postmortem biological fluids. *J Anal Toxicol* 25: 152
- Elliott SP (2004) Further evidence for the presence of GHB in postmortem biological fluid: implications for the interpretation of findings. *J Anal Toxicol* 28: 20-26
- Engberg G and Nissbrandt H (1993) gamma-Hydroxybutyric acid (GHBA) induces pacemaker activity and inhibition of substantia nigra dopamine neurons by activating GABAB receptors. *Naunyn Schmiedeberg's Arch Pharmacol*. 1993 Nov; 348 (5):491-7. *Naunyn Schmiedeberg's Arch Pharmacol* 348 491-497
- Feigenbaum JJ and Howard SG (1996) Naloxone reverses the inhibitory effect of gamma-hydroxybutyrate on central DA release in vivo in awake animals: a microdialysis study. *Neurosci Lett* 218: 5-8
- Feigenbaum JJ and Simantov R (1996) Lack of effect of gamma-hydroxybutyrate on mu, delta and kappa opioid receptor binding. *Neurosci Lett* 212: 5-8
- Ferrara SD, Zotti S, Tedeschi L, et al. (1992) Pharmacokinetics of gamma-hydroxybutyric acid in alcohol dependent patients after single and repeated oral doses. *Br J Clin Pharmacol* 34: 231-235
- Frawly K and McMillan DE (2008) Effects of gamma-hydroxybutyrate on punished responding in pigeons. *Behav Pharmacol* 19: 77-79
- Frye CA, Paris JJ and Rhodes ME (2009) Increasing 3alpha,5alpha-THP following inhibition of neurosteroid biosynthesis in the ventral tegmental area reinstates anti-anxiety, social, and sexual behavior of naturally receptive rats. *Reproduction* 137: 119-128
- Fuller DE, Hornfeldt CS, Kelloway JS, et al. (2004) The Xyrem risk management program. *Drug Saf* 27: 293-306
- Gallimberti L, Schifano F, Forza G, et al. (1994) Clinical efficacy of gamma-hydroxybutyric acid in treatment of opiate withdrawal. *Eur Arch Psychiatry Clin Neurosci* 244: 113-114
- Galloway GP, Frederick-Osborne SL, Seymour R, et al. (2000) Abuse and therapeutic potential of gamma-hydroxybutyric acid. *Alcohol* 20: 263-269
- Galloway GP, Frederick SL, Staggers FE, Jr., et al. (1997) Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence. *Addiction* 92: 89-96
- Geldenhuys FG, Sonnendecker EW and De Klrk MC (1968) Experience with sodium-gamma-4-hydroxybutyric acid (gamma-OH) in obstetrics. *J Obstet Gynaecol Br Commonw* 75: 405-413

- Germain A, Nofzinger EA, Kupfer DJ, et al. (2004) Neurobiology of non-REM sleep in depression: further evidence for hypofrontality and thalamic dysregulation. *Am J Psychiatry* 161: 1856-1863
- Ghodse H, Corkery J, Ahmed K, et al. (2010) Drug-related deaths in the UK. Annual Report 2010. National Programme on Substance Abuse Deaths (np-SAD) International Centre for Drug Policy (ICDP), St George's, University of London, UK
- Gobaille S, Schleef C, Hechler V, et al. (2002) Gamma-hydroxybutyrate increases tryptophan availability and potentiates serotonin turnover in rat brain. *Life Sci* 70: 2101-2112
- Gonzalez A and Nutt DJ (2005) Gamma hydroxy butyrate abuse and dependency. *J Psychopharmacol* 19: 195-204
- Hechler V, Gobaille S, Bourguignon JJ, et al. (1991) Extracellular events induced by gamma-hydroxybutyrate in striatum: a microdialysis study. *J Neurochem* 56: 938-944
- Heinrichs M, Baumgartner T, Kirschbaum C, et al. (2003) Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol Psychiatry* 54: 1389-1398
- Heuser I, Yassouridis A and Holsboer F (1994) The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. *J Psychiatr Res* 28: 341-356
- Holsboer F and Ising M (2010) Stress hormone regulation: biological role and translation into therapy. *Annu Rev Psychol* 61: 81-109, C101-111
- Ising M, Horstmann S, Kloiber S, et al. (2007) Combined dexamethasone/corticotropin releasing hormone test predicts treatment response in major depression - a potential biomarker? *Biol Psychiatry* 62: 47-54
- Ising M, Kunzel HE, Binder EB, et al. (2005) The combined dexamethasone/CRH test as a potential surrogate marker in depression. *Prog Neuropsychopharmacol Biol Psychiatry* 29: 1085-1093
- Iten PX, Oestreich A, Lips R, et al. (2000) [A new drug reaches Switzerland: coma after intake of gamma-hydroxybutyrate (GHB)]. *Schweiz Med Wochenschr* 130: 356-361
- Janowsky DS, el-Yousef MK, Davis JM, et al. (1972) A cholinergic-adrenergic hypothesis of mania and depression. *Lancet* 2: 632-635
- Judd LL, Paulus MJ, Schettler PJ, et al. (2000) Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am J Psychiatry* 157: 1501-1504
- Kalueff AV and Nutt DJ (2007) Role of GABA in anxiety and depression. *Depress Anxiety* 24: 495-517
- Kantrowitz JT, Citrome L and Javitt DC (2009) A review of tolerability and abuse liability of gamma-hydroxybutyric acid for insomnia in patients with schizophrenia. *Clin Ther* 31 Pt 1: 1360-1373
- Karlsen SN, Spigset O and Slordal L (2008) The dark side of ecstasy: neuropsychiatric symptoms after exposure to 3,4-methylenedioxymethamphetamine. *Basic Clin Pharmacol Toxicol* 102: 15-24
- Kaupmann K, Cryan JF, Wellendorph P, et al. (2003) Specific gamma-hydroxybutyrate-binding sites but loss of pharmacological effects of gamma-hydroxybutyrate in GABA(B)(1)-deficient mice. *Eur J Neurosci* 18: 2722-2730
- Khisti RT and Chopde CT (2000) Serotonergic agents modulate antidepressant-like effect of the neurosteroid 3alpha-hydroxy-5alpha-pregnan-20-one in mice. *Brain Res* 865: 291-300
- Khisti RT, Chopde CT and Jain SP (2000) Antidepressant-like effect of the neurosteroid 3alpha-hydroxy-5alpha-pregnan-20-one in mice forced swim test. *Pharmacol Biochem Behav* 67: 137-143
- Knudsen K, Jonsson U and Abrahamsson J (2010) Twenty-three deaths with gamma-hydroxybutyrate overdose in western Sweden between 2000 and 2007. *Acta Anaesthesiol Scand* 54: 987-992
- Korolev V, Barkhatov VI, Smolianitskii Iu N, et al. (1979) [State of the glucocorticoid function of the adrenal glands in gynecological patients operated on under epidural anesthesia balanced with sodium oxybutyrate]. *Vestn Khir Im I I Grek* 122: 117-120
- Krupitsky EM, Burakov AM, Ivanov VB, et al. (1993) Baclofen administration for the treatment of affective disorders in alcoholic patients. *Drug Alcohol Depend* 33: 157-163
- Kupfer DJ (1978) Application of EEG sleep for the differential diagnosis and treatment of affective disorders. *Pharmakopsychiatr Neuropsychopharmacol* 11: 17-26
- Kurian BT, Greer TL and Trivedi MH (2009) Strategies to enhance the therapeutic efficacy of antidepressants: targeting residual symptoms. *Expert Rev Neurother* 9: 975-984
- Laborit H, Jouany JM, Gerard J, et al. (1960) [Summary of an experimental and clinical study on a metabolic substrate with inhibitory central action: sodium 4-hydroxybutyrate]. *Presse Med* 68: 1867-1869
- Langlois M, Lacrotte J and Ferrier J (1960) Action du g-hydroxybutyrate de sodium sur les syndrome névrotiques et psychopathiques avec agitation psychomotrices. *Agressologie* 1: 431-433

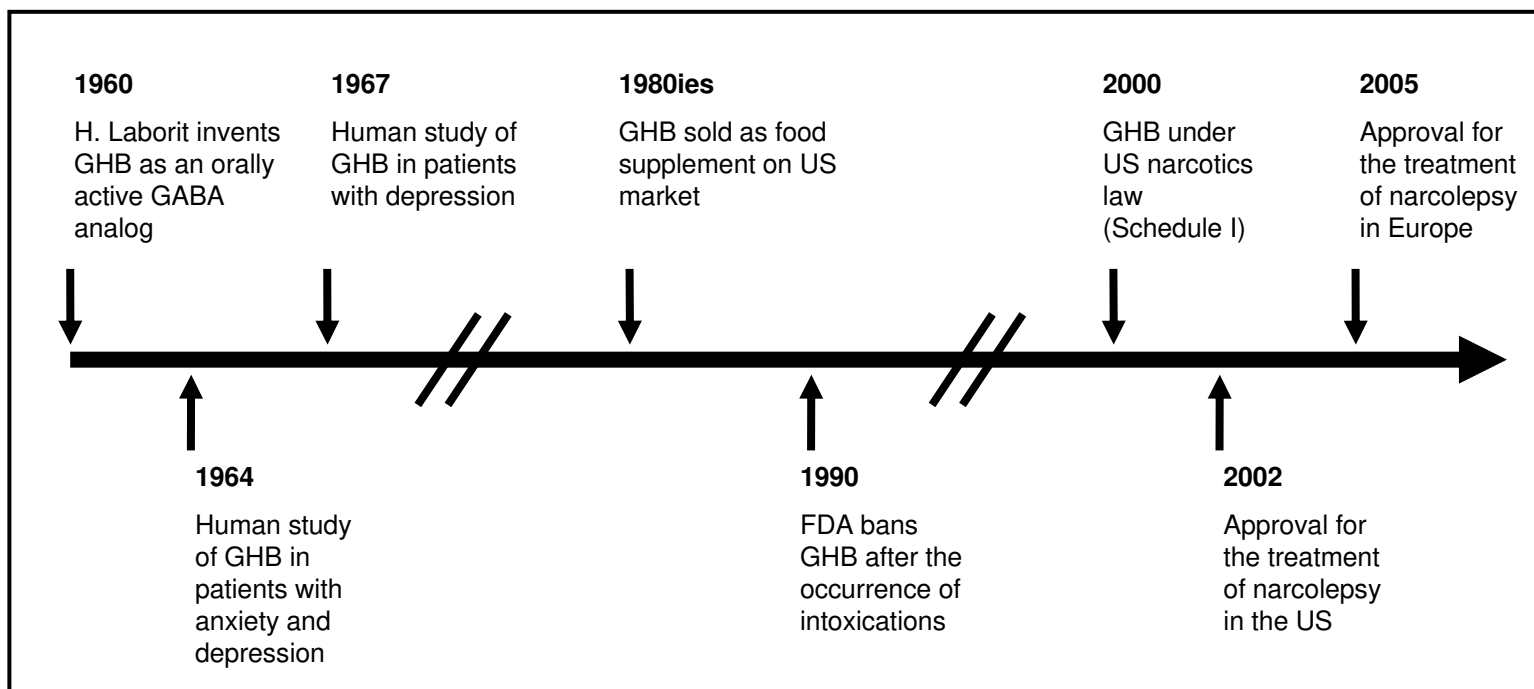


- Lapierre O, Montplaisir J, Lamarre M, et al. (1990) The effect of gamma-hydroxybutyrate on nocturnal and diurnal sleep of normal subjects: further considerations on REM sleep-triggering mechanisms. *Sleep* 13: 24-30
- Lapierre O, Montplaisir J and Poirier G (1989) GHB REM-induction test: a possible biological marker for depression. *Sleep Res* 18: 368
- Legros JJ (2001) Inhibitory effect of oxytocin on corticotrope function in humans: are vasopressin and oxytocin ying-yang neurohormones? *Psychoneuroendocrinology* 26: 649-655
- Leone MA, Vigna-Taglianti F, Avanzi G, et al. (2010) Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. *Cochrane Database Syst Rev*: CD006266
- Maitre M (1997) The gamma-hydroxybutyrate signalling system in brain: organization and functional implications. *Prog Neurobiol* 51: 337-361
- Malyshev VV, Treshchuk LI and Belykh NG (1981) [Evaluation of the protective effect of gamma-hydroxybutyric acid in stress]. *Biull Eksp Biol Med* 91: 537-539
- Mamelak M (2007) Alzheimer's disease, oxidative stress and gammahydroxybutyrate. *Neurobiol Aging* 28: 1340-1360
- Mamelak M (2009) Narcolepsy and depression and the neurobiology of gammahydroxybutyrate. *Prog Neurobiol* 89: 193-219
- Mamelak M, Black J, Montplaisir J, et al. (2004) A pilot study on the effects of sodium oxybate on sleep architecture and daytime alertness in narcolepsy. *Sleep* 27: 1327-1334
- Mamelak M, Escriu JM and Stokan O (1973) Sleep-inducing effects of gammahydroxybutyrate. *Lancet* 2: 328-329
- Mamelak M, Escriu JM and Stokan O (1977) The effects of gamma-hydroxybutyrate on sleep. *Biol Psychiatry* 12: 273-288
- Mathivet P, Bernasconi R, De Barry J, et al. (1997) Binding characteristics of gamma-hydroxybutyric acid as a weak but selective GABAB receptor agonist. *Eur J Pharmacol* 321: 67-75
- McEwen BS (2001) Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. *Ann N Y Acad Sci* 933: 265-277
- McGregor IS, Callaghan PD and Hunt GE (2008) From ultrasocial to antisocial: a role for oxytocin in the acute reinforcing effects and long-term adverse consequences of drug use? *Br J Pharmacol* 154: 358-368
- McMahon LR, Coop A, France CP, et al. (2003) Evaluation of the reinforcing and discriminative stimulus effects of 1,4-butanediol and gamma-butyrolactone in rhesus monkeys. *Eur J Pharmacol* 466: 113-120
- Meerlo P, Westerveld P, Turek FW, et al. (2004) Effects of gamma-hydroxybutyrate (GHB) on vigilance states and EEG in mice. *Sleep* 27: 899-904
- Metcalf DR, Emde RN and Stripe JT (1966) An EEG-behavioral study of sodium hydroxybutyrate in humans. *Electroencephalogr Clin Neurophysiol* 20: 506-512
- Meyer-Lindenberg A (2008) Impact of prosocial neuropeptides on human brain function. *Prog Brain Res* 170: 463-470
- Miotto K, Darakjian J, Basch J, et al. (2001) Gamma-hydroxybutyric acid: patterns of use, effects and withdrawal. *Am J Addict* 10: 232-241
- Morosini PP, Carletti P, Ferretti GF, et al. (1980) [Plasma cortisol levels after acute administration of baclofen]. *Boll Soc Ital Biol Sper* 56: 2428-2431
- Munir VL, Hutton JE, Harney JP, et al. (2008) Gamma-hydroxybutyrate: a 30 month emergency department review. *Emerg Med Australas* 20: 521-530
- Nava F, Premi S, Manzato E, et al. (2007) Gamma-hydroxybutyrate reduces both withdrawal syndrome and hypercortisolism in severe abstinent alcoholics: an open study vs. diazepam. *Am J Drug Alcohol Abuse* 33: 379-392
- Navarro JF, Pedraza C and Gonzalez F (2007) Acute and subchronic effects of gamma-hydroxybutyrate on isolation-induced aggression in male mice. *Methods Find Exp Clin Pharmacol* 29: 379-382
- Nelson T, Kaufman E, Kline J, et al. (1981) The extraneuronal distribution of gammahydroxybutyrate. *Journal of Neurochemistry* 37: 1345-1348
- Nicholson KL and Balster RL (2001) GHB: a new and novel drug of abuse. *Drug Alcohol Depend* 63: 1-22
- Nishino S (2007) Clinical and neurobiological aspects of narcolepsy. *Sleep Med* 8: 373-399
- Ondo WG, Perkins T, Swick T, et al. (2008) Sodium oxybate for excessive daytime sleepiness in Parkinson disease: an open-label polysomnographic study. *Arch Neurol* 65: 1337-1340
- Oyama T, Takiguchi M and Kudo T (1969) Effects of gamma-hydroxybutyrate on plasma levels of ACTH and cortisol in man. *Aggressologie* 10: 411-414
- Palatini P, Tedeschi L, Frison G, et al. (1993) Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *Eur J Clin Pharmacol* 45: 353-356

- Pardi D and Black J (2006) gamma-Hydroxybutyrate/sodium oxybate: neurobiology, and impact on sleep and wakefulness. *CNS Drugs* 20: 993-1018
- Patchev VK, Hassan AH, Holsboer DF, et al. (1996) The neurosteroid tetrahydroprogesterone attenuates the endocrine response to stress and exerts glucocorticoid-like effects on vasopressin gene transcription in the rat hypothalamus. *Neuropsychopharmacology* 15: 533-540
- Patchev VK, Shoaib M, Holsboer F, et al. (1994) The neurosteroid tetrahydroprogesterone counteracts corticotropin-releasing hormone-induced anxiety and alters the release and gene expression of corticotropin-releasing hormone in the rat hypothalamus. *Neuroscience* 62: 265-271
- Pedraza C, Davila G, Martin-Lopez M, et al. (2007) Anti-aggressive effects of GHB in OF.1 strain mice: involvement of dopamine D2 receptors. *Prog Neuropsychopharmacol Biol Psychiatry* 31: 337-342
- Pinna G (2010) In a mouse model relevant for post-traumatic stress disorder, selective brain steroidogenic stimulants (SBSS) improve behavioral deficits by normalizing allopregnanolone biosynthesis. *Behav Pharmacol* 21: 438-450
- Pruessner JC, Dedovic K, Pruessner M, et al. (2010) Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations - 2008 Curt Richter Award Winner. *Psychoneuroendocrinology* 35: 179-191
- Rasmusson AM, Pinna G, Paliwal P, et al. (2006) Decreased cerebrospinal fluid allopregnanolone levels in women with posttraumatic stress disorder. *Biol Psychiatry* 60: 704-713
- Razenberg AJ, Elte JW, Rietveld AP, et al. (2007) A 'smart' type of Cushing's syndrome. *Eur J Endocrinol* 157: 779-781
- Reddy DS (2010) Neurosteroids: endogenous role in the human brain and therapeutic potentials. *Prog Brain Res* 186: 113-137
- Rinaldi F, Puca FM, Mastrosimone F, et al. (1967) [On the use of gamma-hydroxybutyrate of sodium in psychiatric therapy]. *Acta Neurol (Napoli)* 22: 21-41
- Romeo E, Strohle A, Spalletta G, et al. (1998) Effects of antidepressant treatment on neuroactive steroids in major depression. *Am J Psychiatry* 155: 910-913
- Rosen MI, Pearsall HR, Woods SW, et al. (1997) Effects of gamma-hydroxybutyric acid (GHB) in opioid-dependent patients. *J Subst Abuse Treat* 14: 149-154
- Rupprecht R and Holsboer F (1999) Neuroactive steroids: mechanisms of action and neuropsychopharmacological perspectives. *Trends Neurosci* 22: 410-416
- Scantamburlo G, Ansseau M, Geenen V, et al. (2009) Oxytocin: From milk ejection to maladaptation in stress response and psychiatric disorders. A psychoneuroendocrine perspective. *Ann Endocrinol (Paris)* 70: 449-454
- Scharf MB, Baumann M and Berkowitz DV (2003) The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. *J Rheumatol* 30: 1070-1074
- Scharf MB, Lai AA, Branigan B, et al. (1998) Pharmacokinetics of gamma-hydroxybutyrate (GHB) in narcoleptic patients. *Sleep* 21: 507-514
- Schmidt-Mutter C, Pain L, Sandner G, et al. (1998) The anxiolytic effect of gamma-hydroxybutyrate in the elevated plus maze is reversed by the benzodiazepine receptor antagonist, flumazenil. *Eur J Pharmacol* 342: 21-27
- Schmidt C, Gobaille S, Hechler V, et al. (1991) Anti-sedative and anti-cataleptic properties of NCS-382, a gamma-hydroxybutyrate receptor antagonist. *Eur J Pharmacol* 203: 393-397
- Schule C (2007) Neuroendocrinological mechanisms of actions of antidepressant drugs. *J Neuroendocrinol* 19: 213-226
- Schule C, Eser D, Baghai TC, et al. (2010) Neuroactive steroids in affective disorders: target for novel antidepressant or anxiolytic drugs? *Neuroscience*
- Schule C, Eser D, Baghai TC, et al. (2011) Neuroactive steroids in affective disorders: target for novel antidepressant or anxiolytic drugs? *Neuroscience*
- Schule C, Romeo E, Uzunov DP, et al. (2006) Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3alpha-hydroxysteroid dehydrogenase activity. *Mol Psychiatry* 11: 261-272
- Schwartz TL (2007) Gamma hydroxy butyric acid and sodium oxybate used to treat posttraumatic stress disorder. *CNS Spectr* 12: 884-886
- Sgaravatti AM, Magnusson AS, Oliveira AS, et al. (2009) Effects of 1,4-butanediol administration on oxidative stress in rat brain: study of the neurotoxicity of gamma-hydroxybutyric acid in vivo. *Metab Brain Dis* 24: 271-282
- Sgaravatti AM, Sgarbi MB, Testa CG, et al. (2007) Gamma-hydroxybutyric acid induces oxidative stress in cerebral cortex of young rats. *Neurochem Int* 50: 564-570

- Shiromani PJ, Gillin JC and Henriksen SJ (1987) Acetylcholine and the regulation of REM sleep: basic mechanisms and clinical implications for affective illness and narcolepsy. *Annu Rev Pharmacol Toxicol* 27: 137-156
- Snead OC, 3rd (2000) Evidence for a G protein-coupled gamma-hydroxybutyric acid receptor. *J Neurochem* 75: 1986-1996
- Snead OC, 3rd and Morley BJ (1981) Ontogeny of gamma-hydroxybutyric acid. I. Regional concentration in developing rat, monkey and human brain. *Brain Res* 227: 579-589
- Sporer KA, Chin RL, Dyer JE, et al. (2003) Gamma-hydroxybutyrate serum levels and clinical syndrome after severe overdose. *Ann Emerg Med* 42: 3-8
- Steiger A and Kimura M (2010) Wake and sleep EEG provide biomarkers in depression. *J Psychiatr Res* 44: 242-252
- Stein DJ (2009) Oxytocin and vasopressin: social neuropeptides. *CNS Spectr* 14: 602-606
- Sumnall HR, Woolfall K, Edwards S, et al. (2008) Use, function, and subjective experiences of gamma-hydroxybutyrate (GHB). *Drug Alcohol Depend* 92: 286-290
- Szabo ST, Gold MS, Goldberger BA, et al. (2004) Effects of sustained gamma-hydroxybutyrate treatments on spontaneous and evoked firing activity of locus coeruleus norepinephrine neurons. *Biol Psychiatry* 55: 934-939
- Trivedi MH, Rush AJ, Wisniewski SR, et al. (2006) Evaluation of outcomes with citalopram for depression using measurement-based care in STAR\*D: implications for clinical practice. *Am J Psychiatry* 163: 28-40
- Uvnas-Moberg K (1998) Antistress Pattern Induced by Oxytocin. *News Physiol Sci* 13: 22-25
- Uzunova V, Sheline Y, Davis JM, et al. (1998) Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. *Proc Natl Acad Sci U S A* 95: 3239-3244
- Van Cauter E, Plat L, Scharf MB, et al. (1997) Simultaneous stimulation of slow-wave sleep and growth hormone secretion by gamma-hydroxybutyrate in normal young Men. *J Clin Invest* 100: 745-753
- van Noorden MS, van Dongen LC, Zitman FG, et al. (2009) Gamma-hydroxybutyrate withdrawal syndrome: dangerous but not well-known. *Gen Hosp Psychiatry* 31: 394-396
- Van Sassenbroeck DK, De Neve N, De Paepe P, et al. (2007) Abrupt awakening phenomenon associated with gamma-hydroxybutyrate use: a case series. *Clin Toxicol (Phila)* 45: 533-538
- Vescovi PP and Coiro V (2001) Different control of GH secretion by gamma-amino- and gamma-hydroxy-butyric acid in 4-year abstinent alcoholics. *Drug Alcohol Depend* 61: 217-221
- Vienne J, Bettler B, Franken P, et al. (2010) Differential effects of GABAB receptor subtypes, {gamma}-hydroxybutyric Acid, and Baclofen on EEG activity and sleep regulation. *J Neurosci* 30: 14194-14204
- Volpi R, Chiodera P, Caffarra P, et al. (2000) Muscarinic cholinergic mediation of the GH response to gamma-hydroxybutyric acid: neuroendocrine evidence in normal and parkinsonian subjects. *Psychoneuroendocrinology* 25: 179-185
- Wang YG, Swick TJ, Carter LP, et al. (2009) Safety overview of postmarketing and clinical experience of sodium oxybate (Xyrem): abuse, misuse, dependence, and diversion. *J Clin Sleep Med* 5: 365-371
- Wedin GP, Hornfeldt CS and Ylitalo LM (2006) The clinical development of gamma-hydroxybutyrate (GHB). *Curr Drug Saf* 1: 99-106
- Windle RJ, Kershaw YM, Shanks N, et al. (2004) Oxytocin attenuates stress-induced c-fos mRNA expression in specific forebrain regions associated with modulation of hypothalamo-pituitary-adrenal activity. *J Neurosci* 24: 2974-2982
- Wojtowicz JM, Yarema MC and Wax PM (2008) Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. *Cjem* 10: 69-74
- Wong CG, Gibson KM and Snead OC, 3rd (2004) From the street to the brain: neurobiology of the recreational drug gamma-hydroxybutyric acid. *Trends Pharmacol Sci* 25: 29-34
- Woolverton WL, Rowlett JK, Winger G, et al. (1999) Evaluation of the reinforcing and discriminative stimulus effects of gamma-hydroxybutyrate in rhesus monkeys. *Drug Alcohol Depend* 54: 137-143
- Xyrem-International (2005) A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *J Clin Sleep Med* 1: 391-397
- Xyrem-US (2002) A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep* 25: 42-49
- Xyrem-US (2003) The abrupt cessation of therapeutically administered sodium oxybate (GHB) does not cause withdrawal symptoms. *J Toxicol Clin Toxicol* 41: 131-135

- Zak PJ, Stanton AA and Ahmadi S (2007) Oxytocin increases generosity in humans. PLoS One 2: e1128
- Zerbib R, Pierrefiche G, Ferran C, et al. (1992) Potential antidepressant activity of gamma-hydroxybutyrate in the mouse "behavioral despair" test: correlation with the central dopaminergic system. Res Commun Psychol Psychiat Behav 17: 109-122
- Zvosec DL, Smith SW and Hall BJ (2009) Three deaths associated with use of Xyrem. Sleep Med 10: 490-493
- Zvosec DL, Smith SW, Porrata T, et al. (2010) Case series of 226 gamma-hydroxybutyrate-associated deaths: lethal toxicity and trauma. Am J Emerg Med 29: 319-332



**Figure 1** Timeline of medical use of GHB and its legal situation in the US and Europe